Claims 1-13, 22 and 23 stand rejected.

Applicants have cancelled claim 22 to expedite prosecution of the present application. Cancellation of the claims is expressly without waiver of applicants' right to file and prosecute to allowance claims relating to the cancelled subject matter in a divisional or continuation application.

Applicants appreciate the consideration given by the Examiner during the telephonic interview on February 11, 1999. During the interview the Examiner agreed to consider claims amended to specifically recite that applicants' claimed method includes expanding the population of dendritic cell precursors.

In addition to amending claim 1, regarding expansion of the cell population as described below, applicants have also substituted "proportion" for "production". This amendment is supported by claim 1 as originally filed, and the recitation of "proportion" was used by the Examiner in her suggestion of language for claim 1 in the October 19, 1995 Office Action (page 7).

Rejection Under 35 U.S.C. §103

All of the claims remain rejected under 35 U.S.C.§103, because the Examiner continues to contend that Markowicz et al. "appears to disclose" the production of mature dendritic cells from a composition containing dendritic cell precursors. Applicants disagree with the Examiner's interpretation of Markowicz et al. However, applicants' present amendment to claim 1 further clarifies the distinction and nonobviousness of the claimed invention.

Applicants have amended claim 1 to specifically recite that the tissue source is cultured on a substrate and in culture medium so as to expand the number of dendritic cell precursors by allowing the dendritic cell precursors to proliferate. This amendment clarifies the distinction between the claimed invention and Markowicz et al. since Markowicz et al. teaches away from expanding the population of dendritic cells through the proliferation of precursor cells. Support for this amendment is present in the application which recites that the "growth medium for the cells at each step of the method of the invention should allow for the survival and proliferation of the precursor dendritic cells" (page 29, lines 21-23). In addition, the specification recites that "[t]o further expand the blood derived population of dendritic cells, cell aggregates may be serially subcultured multiple times at intervals which provide for the continued proliferation of dendritic cell precursors" (page 35, lines 25-27) and that "[a] panel of monoclonal antibodies may be used to identify and characterize the cells in the GM-CSF expanded cultures." Page 37, lines 17-18. Applicants' specification therefore clearly discloses that by providing methods for causing the proliferation of dendritic cell precursors, applicants have also provided a method for expanding the population of such cells and the cells into which they mature.

In contrast to applicants' invention for expanding populations of dendritic cell precursors, Markowicz et al. states

> As shown in Fig. 4. the number of differentiated (branched) DC increased as the concentration of GM-CSF in the culture increased. At any given concentration of the cytokine, however, the total number of viable cells as well as the number of branched cells per well remained stable over time suggesting that GM-CSF does not cause DC to divide and proliferate.

Markowicz et al., page 958, emphases added. The statement by Markowicz et al. that the "total number of viable cells as well as the number of branched cells per well remained stable over time" and that this result suggests that "GM-CSF does not cause DC to divide and proliferate" clearly does not provide any basis for suggesting that the population of dendritic cell precursors and subsequent mature dendritic cells could be expanded by allowing the precursors to proliferate.

Figure 4 of Markowicz et al. shows the lack of an increase in dendritic cell number over time as changes in the number of branched cells/well are insignificant from day 11 to day 24. Clearly, if a population of dendritic cells were proliferating and expanding as claimed by Applicants, this number should increase over time. This is in stark contrast to Applicants' invention which demonstrates expansion of dendritic cell cultures from proliferating dendritic cell precursors. As stated by Applicants:

> In summary, from a starting blood mononuclear culture of 1.5×10^6 cells, where dendritic cells were difficult to detect, we on average obtained 5-10 subcultures <u>each</u> with at least $3\text{-}10 \times 10^4$ released dendritic cells at 3 weeks, as well as many aggregates capable of further proliferation.

Page 52, line 33 – page 53, line 3. Applicants' invention is therefore clearly not made obvious by Markowicz et al., as Markowicz et al. provides no evidence of proliferating dendritic cell precursors which cause an expansion in the number of dendritic cell precursors and subsequent mature dendritic cells.

In view of the above amendments and remarks, Applicants respectfully request reconsideration and removal of all remaining grounds of rejection and allowance of the pending claims.

Respectfully submitted,

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Dated: February 22, 1999

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on Feb. 22, 1999

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